PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P680PC00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00542	International filing date *(day/month/year)* 14.08.2003	Priority date *(day/month/year)* 15.08.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/47		
Applicant LEUKOTECH A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.03.2004	09.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Herrero, M Telephone No. +49 89 2399-8542

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00542

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-42, 51 as originally filed

Sequence listings part of the description, Pages

1-151 as originally filed

Claims, Numbers

1-73 as originally filed

Drawings, Sheets

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 67 and 70

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 67 and 70 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 67 and 70 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 67 and 70

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 21, 23-35, 37, 38, 40, 42, 44, 50, 53-56, 60-63, 65, 69, 71, 72
	No:	Claims	1, 2, 4-20, 22, 36, 39, 41, 43, 45-49, 51, 52, 57-59, 64, 66, 68, 73
Inventive step (IS)	Yes:	Claims	60-63, 65, 69, 71, 72
	No:	Claims	1-59, 64, 66, 68, 73
Industrial applicability (IA)	Yes:	Claims	1-66, 68, 69, 71-73
	No:	Claims	

2. Citations and explanations

   see separate sheet

SECTION I

6. Additional observations

It seems that the page on which Table I appears should have been numerated as description page 43 (and not as page 51 subsequent to the claim pages).

SECTION III

As a consequence of the clarity and/or sufficiency of disclosure deficiencies within the meaning of Art. 6 PCT and/or Art. 5 PCT which affect the subject-matter encompassed by present independent Claims 67 and 70, the International Search Report (ISR) has not been established in respect of said Claims 67 and 70 (see explanations on Form PCT/ISA/210).

The present International Preliminary Examining Authority (IPEA) agrees with the aforementioned objections set forth in the ISR and notes that claims, or parts of claims, relating to inventions in respect of which no ISR has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). Accordingly the present preliminary report has only been established for the subject-matter in respect of which an ISR has been drawn (Rule 70.2(d) PCT).

The applicant is additionally advised that the EPO policy when acting as an IPEA is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

SECTION IV

In view of the cited prior art relevant to the present application an objection as to lack of unity of invention (Rule 13 PCT) has been raised in the ISR in respect of the subject-matter claimed, i.e. instant Claims 1-73 (see explanations on Form PCT/ISA/210).

In agreement with the reasoning provided in the ISR, the present IPEA notes that within the group of peptides covered by Claims 1-52 previously known peptides are included, and that the therapeutic use of such peptides, for instance, in the treatment of bacterial infections or sepsis, has been also disclosed (see below).

The special technical feature of each of the peptides that makes a contribution over the prior art (Rule 13.2 PCT) is the specific sequence of the peptide. From this special technical feature the objective problem to be solved by this and all further inventions is to provide alternative peptides. Therefore, each of the claimed peptides constitutes one invention.

If a group of the hereby claimed peptides would share the same function (e.g. pro-inflammatory peptides, anti-inflammatory peptides, peptides which could be used for the prevention of cell apoptosis, etc) and if this function would constitute a special technical feature making a contribution over the prior art (Rule 13.2 PCT), such peptides could possibly be grouped as one invention according to their use/function. However, no apparent grouping of the peptides appears to be feasible given the information disclosed in the description. As it is not evident which sequence has which function, the peptides cannot be grouped according to any logical distribution (cf discussion on Form PCT/ISA/210).

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 The following documents have been considered for the purposes of this report:

D1: US-A-6107460
D2: Pereira, H.A. et al (1993) Proc. Natl. Acad. Sci. USA **90**:4733-4737 (also cited in the application)
D3: US-A-560392
D4: WO 93/19087
D5: D'Cruz, O.J. et al (1995) **J.** Andrology **16**:432-440
D6: Shrotri, M.S. et al (2000) **J.** Surg. Res.**89**:53-39 (also cited in the application)

2.2 Novelty and inventive step (Art. 33(2) and (3) PCT)

The present application does not satisfy the criteria set forth in Article 33(2) and (3) PCT because,

a) the subject-matter of Claims 1, 2, 4-20, 22, 36, 39, 41, 43, 45-49, 51, 52, 57-59, 64, 66, 68 and 73 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT)

b) the subject-matter of Claims 1-59, 64, 66, 68 and 73 does not involve an inventive step (Rule 65(1)(2) PCT).

The application pertains to peptide fragments derived from the sequence of heparin-binding protein (HBP) and/or human neutrophil elastase and therapeutic applications thereof (HBP is also known in the art as 37-kDa cationic antimicrobial protein, i.e. CAP 37, or azurocidin).

A peptide with a sequence identical to the corresponding amino acid sequence of the peptide identified in present Claim 36 is known from D2 (cf elastase peptide 20-44 shown in Fig. 6 on page 4736). This peptide sequence falls under the sequence scope of the peptides defined in present Claims 1, 4-7, 11, 13-15, 17, 18, 36, 48 and 51. Hence said Claims 1, 4-7, 11, 13-15, 17, 18, 36, 48 and 51 encompass subject-matter that is neither novel nor inventive, contrary to Art. 33(2) and (3) PCT.

On the other hand, a peptide with a sequence identical to the corresponding amino acid sequence of the peptide identified in present Claim 39 is known from D1 (cf SEQ ID NO:1), D2 (cf CAP37 peptide 20-44 shown in Fig. 6 on page 4736), D3 (cf SEQ ID NO:1) and D4 (cf SEQ ID NO:8). This peptide sequence falls under the sequence scope of the peptides according to present Claims 1, 2, 4-20, 22, 39, 41, 45, 46, 47, 49 and 52. Said Claims 1, 2 , 4-20, 22, 39, 41, 45, 46, 47, 49 and 52 therefore also encompass subject-matter that is neither novel nor inventive, contrary to Art. 33(2) and (3) PCT.

From the point of view of the person skilled in the art the process for the production of a peptide of interest defined in present Claims 55-56 merely represent a routine approach based on conventional working steps. Thus, no inventive contribution as required by Art. 33(3) PCT associated with these procedures is recognizable insofar as the subject peptides to be produced may themselves be non-novel or non-inventive (see above).

The potential therapeutical applicability of the peptide identified in present Claim 39 for the treatment of bacterial infections and septic shock in a mammal is well known from the prior art, e.g. from D1/D4 and D3, respectively.

In addition to its bactericidal effect (against both Gram negative and positive bacteria), D4 teaches the potential applicability of bioactive peptides derived from human CAP 37 protein (cf page 54, lines 30-32 bridging over page 55-56 and 57 lines 1-2) for treating other diseases such as cancers (cf page 63, lines 15-19 and page 64, lines 8 and 25) or any disease involving monocyte localization (cf page 64, lines 6-14), for instance, rheumatoid arthritis or systemic lupus erythematosus (two apparent auto-immune conditions).

Moreover, the bioactive fragment corresponding to peptide 20-44 of the 37-kDa cationic antimicrobial protein (CAP 37) is shown in D5 to be endowed with sperm immobilizing properties but to lack cytotoxicity.

Furthermore, it has been previously established (see e.g. D6) that human HBP not only increases the proinflammatory response of monocytes (e.g. it potentiates the endotoxin-induced release of TNFα and IL-6 from isolated monocytes) but also decreases apoptosis in human and murine neutrophils.

Taking into consideration the teachings of the related prior art referred to above, neither the therapeutic applications intended in present Claims 57-59, 64, 66, 68 nor the pharmaceutical composition pursued in Claim 73 appear to satisfy the novelty and/or inventive step criteria set forth by Arts. 33(2) and (3) PCT.

Notwithstanding the foregoing objections, present Claims 60, 61, 62, 63, 65, 69, 71 and 72 relate to medical uses that in principle seem to be neither disclosed nor rendered obvious by the available prior art. Claims 60, 61, 62, 63, 65, 69, 71 and 72 would therefore appear to fulfill the requirements of Arts. 33(2) and (3) PCT (however see item 2.3(i) below).

2.3 Further comments

(i) On page 27, lines 24-35 bridging over pages 28-29 and page 30, lines 1-23 the description refers to the pharmaceutical interest as drug candidates for different medical applications of monofunctional HBP peptides endowed with desirable characteristic properties. The explanations given with regard to said monofunctional HBP peptides (see e.g. page 28, lines 26-31 and Table 1; page 29, lines 4-7; and page 30, lines 15-18) appear to be of a mere predictive value but do not establish that the expected results have been achieved, i.e. the identification of specific monofunctional HBP peptides useful for some of the pursued therapeutic purposes is not demonstrated.

Based on a number of straightforward hypothetical premises and employing screening assays well known to the person skilled in the art, the experimental section on pages 35-38 bridging over page 39, lines 1-7 generally teaches how to identify active HBP peptide sequences of interest (e.g. peptide sequences with improved binding affinity for bacterial endotoxins or with increased anti-apoptotic activity). Nevertheless, no novel and inventive peptide sequence is eventually characterized.

On the other hand, the substantiating experimental results presented in Examples 3-5 relate to known bioactive peptides (i.e. human HBP 20-44 and porcine HBP 20-44).

It would therefore appear that the invention encompassed by present Claims 60-63, 65, 69 and 71-72 is not adequately supported in the description by information of a technical nature and not sufficiently disclosed in the full width of the scope of the claims, contrary to the requirements of Art. 6 PCT and/or Art. 5 PCT.

(ii) Claims 53 and 54 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. Both claims broadly refer to the same peptides ("the peptide according to any of the claims 1-52") but pursue opposite goals, i.e. inhibiting *versus* stimulating the secretion of cytokine Il-6 from monocytes. Hence, Claims 53 and 54 attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

(iii) Similarly, in view of the opposite purposes of the medicaments referred to in present Claims 64 and 65, the generic formulation of these claims (where both claims rely on the peptides as defined in any of the claims 1-52) introduces ambiguity, contrary to the requirements of Art. 6 PCT.

(iv) It would appear that page 10, line 31 was meant to read "... an anti-inflammatory peptide...".

(v) The scope of dependent Claims 4-22 is rendered unclear, as each one of said claims relies on itself and on its subsequent claim (Art. 6 PCT).

(vi) Figure 6 seems to show what is indicated to be shown in Figure 5.

(vii) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3-D5 is not mentioned in the description, nor are these documents identified therein.